CASE REPORTS

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Ibuprofen-Associated Aseptic Meningitis in Systemic Lupus Erythematosus

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IBUPROFEN (Motrin), a nonsteroidal anti-inflammatory drug of the propionic acid group, is now frequently used in inflammatory musculoskeletal disorders, including systemic lupus erythematosus (SLE). Central nervous manifestations in SLE are highly variable and frequently present problems in diagnosis and management. Recently Widener and Littman[1,2] reported three cases in which ibuprofen may have contributed to aseptic meningitis in SLE. Wasner[3] has also suggested this association in one case. Here we report an additional case in which fever, myalgia, headache and mental confusion were temporally related to ibuprofen ingestion.

Report of a Case

A 21-year-old single white woman visited her physician in October 1974, with complaint of fatigue, fever and multiple pains in the joints. The patient's erythrocyte sedimentation rate (ESR) was 44 mm per hour, antinuclear antibody studies and lupus erythematosus cell preparation were positive, and findings from other studies showed no abnormalities. Aspirin was prescribed but discontinued as a result of tinnitus and gastrointestinal irritation. Ibuprofen therapy, 300 mg four times a day, was begun but was also discontinued because of gastrointestinal irritation, headache, and exacerbation of arthralgia and fever. The patient's condition then gradually improved until six months later when she was first seen in the Arthritis Clinic, University of Utah Medical Center; complaints included a temperature of up to 40°C (104°F); pain in the fingers, wrists and knees; increased fatigability, and a photosensitive skin rash. Physical examination showed no abnormalities except for swelling, heat and tenderness in the wrists, metacarpal phalangeal and proximal interphalangeal joints. No rash, alopecia, Raynaud phenomenon, pleuritis, pericarditis or neurologic abnormalities were present. Findings on a hemogram and on analysis of urine were within normal limits, the ESR was only slightly elevated at 27 mm per hour by the Westergren method, antinuclear antibody studies were positive and a rheumatoid latex fixation test was negative. Serum C3 and C4 were within normal limits. The previous diagnosis of systemic lupus erythematosus was supported by these results and the patient was treated with aspirin, 650 mg four times a day. Approximately one month later, increasing pain in the joints and stiffness and swelling of the left knee occurred. An erythematous rash appeared on the face and body and therapy with hydroxychloroquine sulfate was started, 200 mg twice a day. The patient's symptoms were progressive and prednisone therapy, 5 mg per day, was started in May 1975, with improvement in symptoms. Prednisone therapy was stopped in August 1975 and, except for mild arthritis, symptoms resolved.

On February 12, 1976, increasing fatigue developed, along with painful swelling of the patient's feet, knees, fingers and wrists. The patient said that fever, rash, headache or other symptoms had not occurred. Results of examination showed an effusion in the left knee and tenderness with painful motion of the shoulders and right knee. Analysis of urine showed no abnormalities, hematocrit was 41 percent, leukocyte count was 5,200 per cu mm with normal differential, and the ESR was 31 mm per hour. Ibuprofen, 400 mg four times a day, was prescribed, and on February 13, 1976, the patient was admitted to the University of Utah hospital after several hours of fever, headache, nausea and vomiting, which began

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shortly after administration of ibuprofen. The patient's temperature was 37.7°C (100°F), pulse rate was 100 and blood pressure was normal. Examination of the joints showed no changes, but there was a painful stiffness in the neck with no localized neurological findings. A lumbar puncture was done and analysis of the cerebrospinal fluid showed 50 nucleated cells per cu mm, of which 21 were polymorphonuclear neutrophils; the glucose value was 43 mg per dl (serum glucose, 114 mg per dl) and the protein level was 59 mg per dl. The Gram stain and India ink preparation were negative. While cultures were being done, therapy with penicillin G, 2 million units given intravenously every four hours, was started and ibuprofen therapy was stopped. Four days later, findings from a second lumbar puncture showed 15 mononuclear cells per cu mm and normal protein and glucose levels. Counterimmune electrophoresis was negative for pneumococcal, meningococcal and hemophilus influenza type B antigens. The cultures remained negative and the findings seemed consistent with aseptic meningitis. Administration of antibiotics was discontinued. The patient's condition improved and she was discharged, on a regimen of aspirin and hydroxychloroquine sulfate.

She was seen one week later in clinic and physical examination showed no abnormalities except arthritis; as a result, ibuprofen was prescribed again but was not taken by the patient until February 24, 1978. Headache, nausea, and vomiting developed within hours and the patient was taken to the emergency room at the University of Utah Medical Center. On examination she had a temperature of 38.1°C (100.6°F) but vital signs and nuchal rigidity were normal. Neurological examination showed no localizing signs but the patient was moderately obtunded. Results of a lumbar puncture showed 3,300 nucleated cells per cu mm with 99 percent polymorphonuclear neutrophils. Gram stain and counterimmune electrophoresis for pneumococcal, meningococcal and hemophilus influenza type B antigens were negative. The cerebrospinal fluid glucose value was 10 mg per dl (serum glucose, 152 mg per dl). A probable diagnosis of bacterial meningitis was made and therapy with high doses of penicillin, given intravenously, was started. The obtundation gradually cleared and the cerebrospinal fluid returned to normal in one week. All cultures were negative. Results from a computed tomography scan were also normal. The question of ibuprofen toxicity was raised because of the temporal relationship of the drug to exacerbations, and appropriate warnings were given. The patient has had no further neurological manifestations in 30 months of follow-up without ibuprofen therapy. The SLE has remained reasonably controlled although she has had recurrent pleuropericardial effusions responsive to aspiration and various increases in oral steroids.

Comment

While central nervous system disturbances are clearly seen in SLE, a presentation consistent with aseptic meningitis is rare.[4,5] Because the diagnosis of aseptic meningitis and central nervous system manifestations of SLE are both made largely on exclusionary grounds, precise diagnosis is difficult. There is evidence that ibuprofen may have been associated with aseptic meningitis in patients with SLE.[1-3] Another case has been reported with similar findings and at least one temporally related challenge with ibuprofen therapy, again resulting in an episode of aseptic meningitis.

Aseptic meningitis induced by drugs other than ibuprofen has been reported,[6-8] but, as in this case, the mechanism of action is not known. The rapid onset of symptoms after the ingestion of ibuprofen in this patient could be a result of a drug-hypersensitivity reaction or direct irritation. Ibuprofen inhibits prostaglandin synthesis,[9] but it is doubtful that this caused aseptic meningitis in this patient. Aspirin, also an inhibitor of prostaglandin synthesis,[9] was ingested by the patient without evidence of the symptoms seen after ibuprofen therapy. It is interesting that drugs of this class have also been shown to decrease renal function in patients with SLE.[10]

Ibuprofen and other chemically related drugs are now commonly used for multiple rheumatic problems, but the aseptic meningitis syndrome has been reported only in patients with SLE who are treated with ibuprofen. While this may represent a unique linkage of drug properties and patient sensitivity, the development of new or changing neurological signs in patients receiving phenylalkanoic acid derivatives warrants careful observation and perhaps reassessment of the therapeutic regimen.

Summary

Ibuprofen is now frequently used in disorders involving inflammatory connective tissue, including systemic lupus erythematosus. Although asep-

tic meningitis is unusual in patients with systemic lupus erythematosus, recently it has been suggested that aseptic meningitis may be induced by the administration of ibuprofen. We report a case in which aseptic meningitis developed in a patient treated with ibuprofen for systemic lupus erythematosus.

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Refer to: Mate TP, Swerdlin AHR, Stone RA, et al: Clonidine hydrochloride withdrawal complicating bilateral nephrectomy. West J Med 131:59-62, Jul 1979

Clonidine Hydrochloride Withdrawal Complicating Bilateral Nephrectomy

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CLONIDINE HYDROCHLORIDE is an effective antihypertensive agent that has been used in the management of moderate to severe hypertension.[1-5] The presumed site of action is at the level of the brain stem where the drug has a stimulatory effect on a vasomotor inhibitory pathway. Activation of this pathway reduces sympathetic vasomotor tone at the periphery and decreases systemic blood pressure.[6-9] Clonidine hydrochloride has also been shown to decrease the secretion of renin.[10,11]

The abrupt cessation of clonidine administration has been reported to cause a syndrome of sympathetic overactivity (Figure 1). Manifestations associated with this syndrome include severe hypertension, tachycardia, headache, anxiety, nausea, vomiting, and an elevation in serum and urinary catecholamines.[12,14]

Renovascular hypertension has been characterized by some authors as resulting in an elevated renin profile and clonidine has been shown to be effective in lowering the blood pressure of these patients. Strauss and co-workers have suggested that there is a greater risk of the clonidine withdrawal syndrome developing in patients with renovascular hypertension.[15] They suggested that this may be due to simultaneous reactivation of the renin-angiotensin and the catecholamine-sympathetic systems. However, the former has never been documented. We recently encountered a severe episode of hypertension in a patient several hours after bilaterial nephrectomy; the patient had been receiving clonidine for several months before administration was discontinued on the day of surgical operation. This case is presented and a mechanism is proposed for clonidine hydrochloride withdrawal syndrome.

Report of a Case

A 23-year-old white man weighing 60 kg (132 pounds), with chronic renal failure and hypertension secondary to proliferation glomerulonephritis, was admitted to hospital for bilateral nephrectomy in preparation for a kidney transplant.

The preoperative course during the previous six months of dialysis had been complicated by accelerated hypertension; this was unresponsive to salt and water depletion, as manifested by a weight loss of 6 kg. Peripheral vein renin values at this time were 240 ng per ml per hour in the supine position and 245 ng per ml per hour in the upright position (normal 0.5 to 7 ng per ml

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